



## FRAX and ethnicity

J. A. Kanis<sup>1,2</sup> · C. Cooper<sup>3,4</sup> · B. Dawson-Hughes<sup>5</sup> · N. C. Harvey<sup>3,6</sup> · H. Johansson<sup>1,2</sup> · M. Lorentzon<sup>1,7</sup> · E. V. McCloskey<sup>2,8</sup> · J.-Y. Reginster<sup>9,10</sup> · R. Rizzoli<sup>11</sup> · on behalf of the International Osteoporosis Foundation

Received: 31 August 2020 / Accepted: 1 September 2020

© International Osteoporosis Foundation and National Osteoporosis Foundation 2020

### Introduction

A recent article from the New England Journal of Medicine questioned the use of race or ethnicity in assessment algorithms [1]. In the case of osteoporosis, the authors noted that the US FRAX calculator returns a lower fracture risk for women who are Black (by a factor of 0.43), Asian (0.50) or Hispanic (0.53). They conclude that the lower risk for Black, Asian and minority ethnic (BAME) women may delay intervention with osteoporosis therapy. The New York Times goes further in stating that with FRAX (sic) Black women end up having a score that makes them less likely to be prescribed osteoporosis medication than white women who are similar in all other respects [2].

In the case of osteoporosis and FRAX, the authors do not appear to have grasped the reality of fracture epidemiology and risk assessment. In this editorial, we set out the key messages from the epidemiology of fracture globally, key considerations in building risk assessment tools, the specific contribution of race/ethnicity and practical considerations related to any move to alter race/ethnicity categorisation or remove them entirely.

### Heterogeneity of fracture risk

Fracture probability varies markedly in different regions of the world due to differences in fracture risk and mortality [3, 4]. In the case of hip fracture, there is a tenfold range in probability

✉ J. A. Kanis  
w.j.pontefract@sheffield.ac.uk; w.j.pontefract@shef.ac.uk

C. Cooper  
cc@mrc.soton.ac.uk

B. Dawson-Hughes  
bess.dawson-hughes@tufts.edu

N. C. Harvey  
nch@mrc.soton.ac.uk

H. Johansson  
helena@statiq.se

M. Lorentzon  
mattias.lorentzon@medic.gu.se

E. V. McCloskey  
e.v.mccloskey@sheffield.ac.uk

J.-Y. Reginster  
jyr.ch@bluewin.ch

R. Rizzoli  
Rene.Rizzoli@unige.ch

<sup>2</sup> Centre for Metabolic Bone Diseases, Medical School, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, UK

<sup>3</sup> MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

<sup>4</sup> NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK

<sup>5</sup> Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA

<sup>6</sup> NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

<sup>7</sup> Geriatric Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

<sup>8</sup> Mellanby Centre for bone research, Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

<sup>9</sup> Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

<sup>10</sup> Chair for Biomarkers of Chronic Diseases, Biochemistry Department, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia

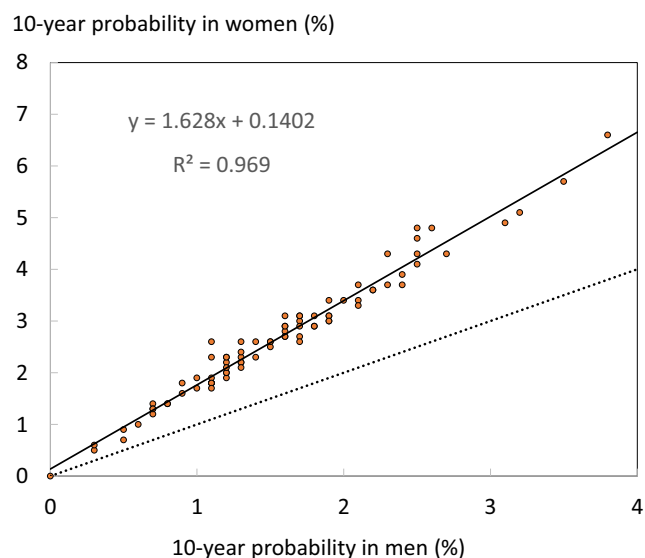
<sup>11</sup> Service of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

<sup>1</sup> Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia

worldwide which far exceeds the differences in incidence between sexes within a country (Fig. 1). Ethnicity is not a direct input variable in the FRAX model; these differences therefore require that FRAX models for a specific country be calibrated to national fracture and mortality rates. Failure to do so would result in exceptionally large and avoidable errors in the stratification of risk. Indeed, it would negate the utility of risk assessment. In addition to 73 country-specific models, ethnicity-specific models are available in the USA, South Africa and Singapore. Variations in ethnicity-specific risk often exceed the differences in risk between sexes. Failure to calibrate for ethnicity would have adverse consequences greater than failure to calibrate for sex.

## Choosing a risk factor

There are a number of factors to be considered in the selection of risk factors for case finding. Of particular importance, in the setting of primary care, is the ease with which they might be used. For a globally applicable tool, the chosen risk factors should also be valid in an international setting and their predictive value stable over time. The use of risk factors for case finding requires that the risk so identified is responsive to a therapeutic intervention. It is important to draw the distinction between reversible risk and reversibility of risk. Age is an example of an irreversible risk factor, but the risk of fracture identified by age has reversibility. Thus, pharmacological intervention has an effect on fracture that is independent of age



**Fig. 1** 10-year probability of hip fracture in men and women age 65 years with a prior fragility fracture in countries where a FRAX model is available. Body mass index set at 25 kg/m<sup>2</sup>. The diagonal dotted line denotes the line of equality. Hip fracture probability in women ranged from 0.5% to more than 5%—a tenfold range. Probabilities in women were on average 65% higher than in men

indicating reversibility of risk [5]. Levels of evidence for the suitability of risk factors have been developed [6, 7]. The efficacy of interventions has been tested worldwide in randomised controlled trials so that ethnicity, race and location have a high level of evidence indicating their suitability for inclusion in risk assessment.

## Understanding ethnicity

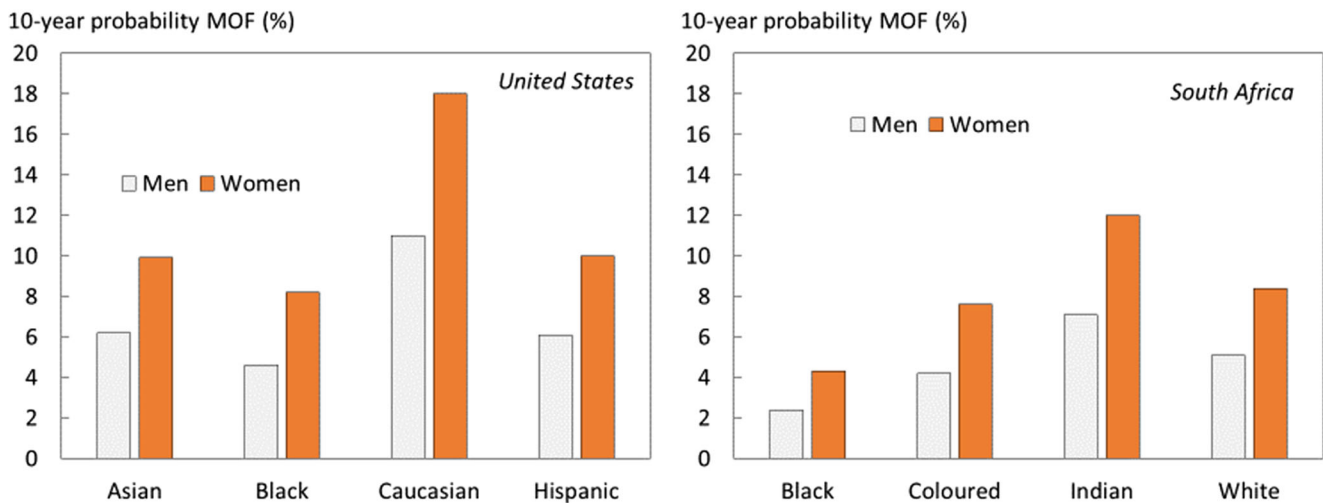
Vyas et al. [1] contest that, if race does correlate with clinical outcomes, this does not necessarily justify its inclusion in diagnostic or predictive tools. Given the complexity of the determinants of race, it is insufficient to translate a data signal into a race adjustment without determining what race might represent in the particular context. Vyas et al. argue that most race corrections implicitly, if not explicitly, operate on the assumption that genetic difference tracks reliably with race. If the empirical differences seen between racial groups were actually due to genetic differences, then race adjustment might be justified: different coefficients for different bodies. Whilst the aspiration that genetics might replace the need for race or ethnicity is worthy [8], its potential in osteoporosis is presently limited and restricted to only a single component of fracture risk (bone mineral density) [9].

The counter argument is that risk factors should be chosen according to established criteria irrespective of our understanding of their basis or their accuracy. A good example is consumption of alcohol, which is notorious for being inaccurately reported. In general, people who drink alcohol tend to neglect or underestimate their alcohol consumption [10, 11]. It matters not whether the return is accurate—only that it provides a consistent indication of risk, which it does. Thus, we are more interested in association than causality. The same goes for race, location and ethnicity.

It is important to recognise that the significance of ethnicity will vary by location. For example, Black people in the USA have lower fracture probabilities than Caucasians [12], but the probability of fracture in USA Black people is much higher than in African Black people [4] in part due to the higher fracture rates and lower mortality risks in those from the USA (Fig. 2). The same holds true for Chinese from Hong Kong, mainland China and Singapore.

## Intervention thresholds

The purpose of FRAX is to characterise fracture risk so that decisions can be facilitated on the need for treatment and, in some instances, the type of treatment [6, 13]. This demands the consideration of intervention thresholds which, in the case of FRAX, is the 10-year probability of fracture above which pharmacological intervention should be considered. Several



**Fig. 2** Ethnic-specific 10-year probabilities of a major osteoporotic fracture in men and women age 65 years with a prior fragility fracture in the USA and South Africa. Body mass index set at 25 kg/m<sup>2</sup>

methods have been used to define intervention thresholds [14] but, in the case of ethnicity-specific models in the USA and Singapore, use thresholds that apply to all ethnicities [15, 16]. Thus, we challenge the view of Vyas et al. [1] that the incorporation of race can exacerbate inequities. Indeed, the converse is true when the gateway to risk assessment is based on BMD testing rather than fracture probability. If the intervention threshold is set at 20% as in North America [16, 17], then the equivalent T-score at age 75 years is  $-2.8$  for Caucasian women but  $-3.8$  for Hispanic and Asian women and  $-4.2$  for Black women. Thus, the use of FRAX as a gateway for intervention helps to resolve, rather than exacerbate, racial inequalities.

## The elephant in the room

A useful measure of health service uptake is the treatment gap which is defined in its simplest form as the number of people with a condition or disease who need treatment for it but who do not get it. The quantification afforded by FRAX has allowed inequalities in the treatment gap to be identified. Shortly after the release of FRAX, it was noted that the treatment gap was substantially wider in Black than white patients at high risk even after adjustment for fracture probability [18, 19]. More recently in the Women's Health Initiative, those at high risk and Asian ethnicity had a much higher likelihood (by 45%) of being on appropriate treatment compared with white women, whilst in Black/African American, there remained almost half the likelihood of appropriate medication use [20]. In addition to racial inequalities, the treatment gap is higher in men than in women [18, 21, 22]. Paradoxically, the therapeutic care gap may be particularly wide in the elderly in whom the importance and impact of treatment are high

[23, 24] and particularly in individuals with fracture who reside in long-term care [25]. It is perhaps ironic that FRAX has permitted these inequalities to be recognised.

In the context of osteoporosis, the major issue is disease discrimination. Many surveys indicate that a small minority of men and women at high fracture risk actually receive treatment [18, 21, 22, 25, 26]. Fewer than 20% of individuals receive therapies to reduce the risk of future fracture within the year following a fracture. Moreover, the treatment gap is increasing with time [22, 26]. The under-treatment of osteoporosis globally has led societies such as the International Osteoporosis Foundation and the American Society for Bone and Mineral Research to come together to urgently address this global crisis in the management of osteoporosis [27–29]. This crisis of undertreatment contrasts with the situation following myocardial infarction, for which condition a significant care gap has been overcome in the past 15 years: 75% of such individuals now receive beta blockers to help prevent recurrent myocardial infarction [30].

Studies to date provide little insight into the causes underlying the substantial and increasing treatment gap. Factors that may play a role in the USA include a decline in BMD testing owing to reimbursement issues and lack of intensive detailing by pharmaceutical companies. Others point the finger at the lay press for raising awareness over the last decade of the potential side effects of the bisphosphonates, such as osteonecrosis of the jaw, atypical femoral fractures and atrial fibrillation [26, 28]. Indeed, many doctors, dentists and patients are now more frightened of the rare but serious side effects than they are of the disease and the fractures that arise. Notwithstanding, the lay press is simply the messenger bringing news and opinion from the scientific community, some or much of which may be ill-judged. The paradox arises in that we seek to treat individual patients to the highest standards but

at the same time disservice and disadvantage the wider osteoporosis community [31]. We should not make the same mistake with ethnicity and risk assessment

## Conclusion

Despite the wide acceptance of the tool, FRAX should not be considered as a gold standard in patient assessment, but rather as a reference platform. Thus, the fracture risk estimates derived from FRAX should not be uncritically used in the management of patients without an appreciation of its limitations as well as its strengths. In some instances, limitations (e.g. to experts in bone disease) are perceived as strengths to others (e.g. primary care physicians) [32, 33]. Notwithstanding, the calibration of country-specific models and, where appropriate, ethnicity-specific intranational models, helps direct treatment to those most at need and avoids unnecessary intervention in those at low risk, amongst all segments of society. However, well intentioned, the NEJM article has the potential to do more harm than good to patients with osteoporosis.

## Compliance with ethical standards

**Competing interests** JAK, NCH, HJ, ML and EVM are responsible for the creation and maintenance of FRAX but derive no financial benefit.

JAK reports no additional competing interests.

CC reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB.

BD-H has received grant support from Pfizer and DSM and consulting fees from TTY Biopharma Co, Ltd, Intrinsic Therapeutics and AgNovos.

NCH has received consultancy/lecture fees/honoraria/grant funding from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Radius Health, Servier, Shire, UCB, Consilient Healthcare and Internis Pharma.

HJ has no conflicts of interest to declare.

ML has received lecture fees from Amgen, Lilly, Meda, Renapharma and UCB Pharma and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma and Consilient Health.

EVM has received consultancy/lecture fees/grant funding/honoraria from AgNovos, Amgen, AstraZeneca, Consilient Healthcare, Fresenius Kabi, Gilead, GSK, Hologic, Internis, Lilly, Merck, Novartis, Pfizer, Radius Health, Redx Oncology, Roche, Sanofi Aventis, UCB, Viiv, Warner Chilcott, and I3 Innovus.

J-YR has received advisory board or consulting fees from IBSA-Genévrier, Pierre Fabre, Radius Health, TEVA and Mylan; lecture fees from Agnovos, IBSA-Genévrier, Mylan, CNIEL, Dairy Research Council (DRC) and Theramex and institutional grant support from IBSA-Genévrier, Mylan, CNIEL and Radius Health.

RR has received consulting fees or advisory board fees from Radius Health, Labatec, Danone, Nestlé, CNIEL and Sandoz.

## References

- Vyas DA, Eisenstein LG, Jones DS (2020) Hidden in plain sight — reconsidering the use of race correction in clinical algorithms. *N Engl J Med* 383:874–882
- Kolata G (2020) Many medical decision tools disadvantage black patients. *New York Times*. <https://www.nytimes.com/2020/06/17/health/many-medical-decision-tools-disadvantage-black-patients.html>. Accessed 28 Aug 2020
- Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Oglesby A (2002) International variations in hip fracture probabilities: implications for risk assessment. *J Bone Miner Res* 17:1237–1244
- Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl DA, Cooper C (2012) A systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporos Int* 23:2239–2256
- Ström O, Lauppe R, Ljunggren Ö, Spångéus A, Ortsäter G, O’Kelly J, Åkesson K (2020) Real-world effectiveness of osteoporosis treatment in the oldest old. *Osteoporos Int* 31:1525–1533
- Kanis JA, on behalf of the World Health Organization Scientific Group (2007) Assessment of osteoporosis at the primary health-care level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK. Available at <http://www.shef.ac.uk/FRAX/index.htm>. Accessed 14 Aug 2020
- Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD (2012) FRAX® with and without BMD. *Calcif Tissue Int* 90:1–13
- Bonham VL, Sellers SL, Gallagher TH, Frank D, Odunlami AO, Price EG, Cooper LA (2009) Physicians’ attitudes toward race, genetics, and clinical medicine. *Genet Med* 11:279–286
- Forgetta V, Keller-Baruch J, Forest M, Durand A, Bhatnagar S, Kemp J, Nethander M, Evans D, Morris JA, Kiel DP, Rivadeneira F, Johansson H, Harvey N, Mellström D, Karlsson M, Cooper C, Evans DM, Clark R, Kanis JA, Orwoll E, McCloskey EV, Ohlsson C, Pineau J, Leslie WD, Greenwood CMT, Richards JB (2020) Development of a polygenic risk score to improve screening for fracture risk: a genetic risk prediction study. *PLoS Med* 17:e1003152. <https://doi.org/10.1371/journal.pmed.1003152>
- Popham RE, Schmidt W (1981) Words and deeds: the validity of self-report data on alcohol consumption. *J Stud Alcohol* 42:355–368
- Watson CG, Tilleskjor C, Hoodecheck-Schow EA, Pucel J, Jacobs L (1984) Do alcoholics give valid self-reports? *J Stud Alcohol* 45:344–348
- Cauley JA, El-Hajj Fuleihan G, Arabi A, Fujiwara S, Ragi-Eis S, Calderon A, Chionh SB, Chen Z, Curtis JR, Danielson ME, Hanley DA, Kroger H, Kung AW, Lesnyak O, Nieves J, Pluskiewicz W, El Rassi R, Silverman S, Schott AM, Rizzoli R, Luckey M, FRAX Position Conference Members (2011) Official positions for FRAX clinical regarding international differences. *J Clin Densitom* 14:240–262
- Kanis JA, Harvey NC, McCloskey E, Bruyère O, Veronese N, Lorentzon M, Cooper C, Rizzoli R, Adib G, Al-Daghri N, Campusano C, Chandran M, Dawson-Hughes B, Javaid K, Jiwa F, Johansson H, Lee JK, Liu E, Messina D, Mkinsi O, Pinto D, Prieto-Alhambra D, Saag K, Xia W, Zakraoui L, Reginster J-Y (2020) Algorithm for the management of patients at low, high and very high risk of osteoporotic fracture. *Osteoporos Int* 31:1–12
- Kanis JA, Harvey NC, Cyrus Cooper C, Johansson H, Odén A, McCloskey EV, the Advisory Board of the National Osteoporosis Guideline Group (2016) A systematic review of intervention thresholds based on FRAX. A report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. *Arch Osteoporos* 11(1):25. <https://doi.org/10.1007/s11657-016-0278-z>
- Kanis JA, Chandran M, Chionh SB, Ganeson G, Harvey NC, Koh WP, Kwok T, Lau TC, Liu E, Lorentzon M, McCloskey EV, Tan KB, Vandenput L, Johansson H (2020b) Use of age-dependent FRAX-based intervention thresholds for Singapore. *Arch Osteoporos* 15(1):104. <https://doi.org/10.1007/s11657-020-00782-9>
- Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R, National Osteoporosis Foundation (2014) Clinician’s

- guide to prevention and treatment of osteoporosis. *Osteoporos Int* 25: 2359–2381 (Erratum *Osteoporos Int* 2015; 26: 2045-7)
17. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, Hanley DA, Hodzman A, Jamal SA, Kaiser SM, Kvern B, Siminoski K, Leslie WD, Scientific Advisory Council of Osteoporosis Canada (2010) 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 182:1864–1873
  18. Curtis JR, McClure LA, Delzell E, Howard VJ, Orwoll E, Saag KG, Safford M, Howard G (2009) Population-based fracture risk assessment and osteoporosis treatment disparities by race and gender. *J Gen Intern Med* 24:956–962
  19. Guggina P, Flahive J, Hooven FH, Watts NB, Siris ES, Silverman S, Roux C, Pfeilschifter J, Greenspan SL, Diez-Pérez A, Cooper C, Compston JE, Chapurlat R, Boonen S, Adachi JD, Anderson FA Jr, Gehlbach S, GLOW Investigators (2012) Characteristics associated with anti-osteoporosis medication use: data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) USA cohort. *Bone* 51:975–980
  20. Sattari M, Cauley JA, Garvan C, Johnson KC, LaMonte MJ, Li W, Limacher M, Manini T, Sarto GE, Sullivan SD, Wactawski-Wende J, Beyth RJ (2017) Osteoporosis in the Women’s Health Initiative: another treatment gap? *Am J Med* 130:937–948
  21. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA (2013) Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos* 8:136. <https://doi.org/10.1007/s11657-013-0136-1>
  22. Borgström F, Karlsson L, Ortsäter G, Norton N, Halbout P, Cooper C, McCloskey EV, Harvey NC, Javaid K, Kanis JA, for the International Osteoporosis Foundation (2020) Fragility fractures in Europe: burden, management and opportunities. *Arch Osteoporos* 15(1):59. <https://doi.org/10.1007/s11657-020-0706-y>
  23. Freedman KB, Kaplan FS, Bilker WB, Strom BL, Lowe RA (2000) Treatment of osteoporosis: are physicians missing an opportunity? *J Bone Joint Surg Am* 82-A:1063–1070
  24. Swedish National Board of Health and Welfare (2009) Quality and efficiency in Swedish Health Care. Swedish Association of Local Authorities and Regions, Swedish National Board of Health and Welfare, Stockholm.
  25. Giangregorio L, Papaioannou A, Cranney A, Zytaruk N, Adachi JD (2006) Fragility fractures and the osteoporosis care gap: an international phenomenon. *Semin Arthritis Rheum* 35:293–305
  26. Solomon DH, Johnston SS, Boytsov NN, McMorro D, Lane JM, Krohn KD (2014) Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. *J Bone Miner Res* 29:1929–1937
  27. Harvey NCW, McCloskey EV, Mitchell PJ, Dawson-Hughes B, Pierroz DD, Reginster J-Y, Rizzoli R, Cooper C, Kanis JA (2017) Mind the (treatment) gap: a global perspective on current and future strategies for prevention of fragility fractures. *Osteoporos Int* 28: 1507–1529
  28. Khosla S, Cauley JA, Compston J, Kiel DP, Rosen C, Saag KG, Shane E (2017) Addressing the crisis in the treatment of osteoporosis: a path forward. *J Bone Miner Res* 32:424–430
  29. Conley RB, Adib G, Adler RA, Åkesson KE, Alexander IM, Amenta KC, Blank RD, Brox WT, Carmody EE, Chapman-Novakofski K, Clarke BL, Cody KM, Cooper C, Crandall CJ, Dirschl DR, Eagen TJ, Elderkin AL, Fujita M, Greenspan SL, Halbout P, Hochberg MC, Javaid M, Jeray KJ, Kearns AE, King T, Koinis TF, Koontz JS, Kužma M, Lindsey C, Lorentzon M, Lyritis GP, Michaud LB, Miciano A, Morin SN, Mujahid N, Napoli N, Oleginski TP, Puzas JE, Rizou S, Rosen CJ, Saag K, Thompson E, Tosi LL, Tracer H, Khosla S, Kiel DP (2020) Secondary fracture prevention: consensus clinical recommendations from a multistakeholder coalition. *J Bone Miner Res* 35:36–52
  30. Austin P, Tu J, Ko D, Alter D (2008) Factors associated with the use of evidence-based therapies after discharge among elderly patients with myocardial infarction. *CMAJ* 179:901–908
  31. Kanis JA, Svedbom A, Harvey N, McCloskey EV (2014) The osteoporosis treatment gap. *J Bone Miner Res* 29:1926–1928
  32. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, Compston J, Dawson-Hughes B, El-Hajj Fuleihan G, Johansson H, Leslie WD, Lewiecki EM, Luckey MM, Oden A, Papapoulos SE, Poiana C, Wahl DA, McCloskey E, and the Task Force of the FRAX Initiative (2011) Interpretation and use of FRAX in clinical practice. *Osteoporos Int* 22:395–411
  33. Kanis JA, Harvey NC, Johansson H, Liu E, Lorentzon M, Leslie WD, Eugene V, McCloskey E (2020) A decade of FRAX: how has it changed the management of osteoporosis? *Aging Clin Exp Res* 32:187–196

**Publisher’s note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.